Notice of Allowability	Application No.	Applicant(s)	
	10/768,976	WOOD ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *an amendment filed on November 3, 2006*.

2. ☒ The allowed claim(s) is/are *35-39,47-51,55,56,58,64-67,69-77,107 and 109-122*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

1. The application has been amended as follows.

The claims are amended as follows.

35. (currently amended) A method to detect or determine the presence or amount of a mutant hydrolase, comprising:

a) contacting a mutant hydrolase with a hydrolase substrate which comprises one or more biotin functional groups, wherein the mutant hydrolase comprises at least one amino acid substitution relative to a corresponding wild-type hydrolase, wherein the at least one amino acid substitution results in the mutant hydrolase forming a bond with the substrate which is more stable than the bond formed between the corresponding wild-type hydrolase and the substrate, wherein the at least one amino acid substitution in the mutant hydrolase is a substitution at an amino acid residue in the corresponding wild-type hydrolase that is associated with activating a water molecule which cleaves the bond formed between the corresponding wild-type hydrolase and the substrate or at an amino acid residue in the corresponding wild-type hydrolase that forms an ester intermediate with the substrate, wherein the wild-type hydrolase is a dehalogenase, wherein the mutant hydrolase is a mutant dehalogenase, and wherein the substrate is a compound of formula (I): ~~linker~~ biotin[[R]]-linker-A-X, wherein the linker is a branched or unbranched carbon chain comprising from 2 to 30 carbon atoms, which chain optionally includes one or more double or triple bonds, and which chain is optionally substituted with one or more hydroxy or oxo (=O) groups, wherein one or more of the carbon atoms in the chain is optionally replaced with a non-peroxide -O-, -S- or -NH-, wherein the linker-A separates biotin[[R]] and X by at least 11 atoms, wherein A-X is a substrate for a dehalogenase, wherein A is $(CH_2)_n$ and n = 2-10, and wherein X is a halogen, and wherein ~~R is a~~ the biotin functional group is coupled through its carboxy terminus to the linker; and

b) detecting or determining the presence or amount of the functional group, thereby detecting or

determining the presence or amount of the mutant dehalogenase.

40 – 44. (canceled)

46. (canceled)

47. (currently amended) A method of labeling ~~to label~~ a cell, comprising:
a) contacting a cell comprising a mutant hydrolase with a hydrolase substrate which comprises one or more biotin functional groups, wherein the mutant hydrolase comprises at least one amino acid substitution relative to a corresponding wild-type hydrolase, wherein the at least one amino acid substitution results in the mutant hydrolase forming a bond with the substrate which is more stable than the bond formed between the corresponding wild-type hydrolase and the substrate, wherein the at least one amino acid substitution in the mutant hydrolase is a substitution at an amino acid residue in the corresponding wild-type hydrolase that is associated with activating a water molecule which cleaves a bond formed between the corresponding wild-type hydrolase and the substrate or at an amino acid residue in the corresponding wild-type hydrolase that forms an ester intermediate with the substrate, wherein the wild-type hydrolase is a dehalogenase, wherein the mutant hydrolase is a mutant dehalogenase, and wherein the substrate is a compound of formula (I): biotin[[R]]-linker-A-X, wherein the linker is a branched or unbranched carbon chain comprising from 2 to 30 carbon atoms, which chain optionally includes one or more double or triple bonds, and which chain is optionally substituted with one or more hydroxy or oxo (=O) groups, wherein one or more of the carbon atoms in the chain is optionally replaced with a non-peroxide -O-, -S- or -NH-, wherein the linker-A separates biotin[[R]] and X by at least 11 atoms, wherein A-X is a substrate for a dehalogenase, wherein A is $(CH_2)_n$ and n = 2-10, wherein X is a halogen, and wherein ~~R is a~~ the biotin functional group is coupled through its carboxy terminus to the linker; and
b) detecting or determining the presence or amount of the functional group.

55. (currently amended) The method of claim 35, ~~40~~ or 47 wherein the linker comprises $(CH_2CH_2)_y$ and y = 2-8.

56. (currently amended) The method of claim 35, ~~40~~ or 47 wherein the linker separates biotin[[R]] and A by at least 12 atoms.

58. (currently amended) The method of any one of claims 35~~, 40~~ or 47 wherein the mutant dehalogenase is present in a cell or on the surface of a cell.

64. (currently amended) The method of any one of claims 35~~, 40~~ or 47 wherein the presence of at least one biotin functional group in a cell is correlated to the subcellular location of the mutant dehalogenase.

107. (currently amended) A method for preparing a compound of the formula biotin[[R]]-Linker-A-X comprising coupling a compound of formula biotin[[R]]-Y with a compound of formula Z-Linker-A-X, wherein Y and Z are groups that can react to link biotin[[R]] to –Linker-A-X, wherein the linker is a branched or unbranched carbon chain comprising from 2 to 30 carbon atoms, which chain optionally includes one or more double or triple bonds, and which chain is optionally substituted with one or more hydroxy or oxo (=O) groups, wherein one or more of the carbon atoms in the chain is optionally replaced with a non-peroxide -O-, -S- or -NH-, wherein the linker-A separates biotin[[R]] and X by at least 11 atoms, wherein A-X is a substrate for a dehalogenase, wherein A is $(CH_2)_n$ and n = 2-10, wherein X is a halogen, wherein ~~R is a~~ biotin is a functional group ~~that~~ is capable of being coupled through its carboxy terminus to the linker, and wherein biotin[[R]]-Y is an activated ester of biotin ~~a compound of formula R~~ and wherein Z is an amine suitable to react with the activated ester to form an amide bond.

109. (currently amended) A method for preparing a compound of the formula biotin[[R]]-Linker-A-X wherein the Linker comprises an amide bond comprising coupling a corresponding activated ester with a corresponding amine to provide the compound of formula biotin[[R]]–Linker-A-X, wherein biotin[[R]] is a ~~biotin~~ functional group, wherein the linker is a branched or unbranched carbon chain comprising from 2 to 30 carbon atoms, which chain optionally includes one or more double or triple bonds, and which chain is optionally substituted with one or more hydroxy or oxo (=O) groups, wherein one or more of the carbon atoms in the chain is optionally replaced with a non-peroxide -O-, -S- or -NH-, wherein A-X is a substrate for a dehalogenase, wherein A is $(CH_2)_n$ and n = 2-10, and wherein X is a halogen.

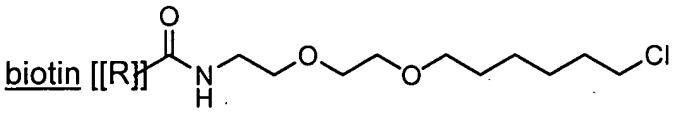
110. (currently amended) A compound of formula (I): biotin[[R]]-linker-A-X, wherein biotin[[R]] is a ~~one or more~~ functional group[[s]], wherein the linker is a branched or unbranched carbon

chain comprising from 2 to 30 carbon atoms, which chain optionally includes one or more double or triple bonds, and which chain is optionally substituted with one or more hydroxy or oxo (=O) groups, wherein one or more of the carbon atoms in the chain is optionally replaced with a non-peroxide -O-, -S- or -NH-, wherein the linker-A separates biotin[[R]] and X by at least 11 atoms, wherein A is $(CH_2)_n$ and n = 4-10, wherein A-X is a substrate for a dehalogenase, and wherein X is a halogen, wherein ~~R is a~~ the biotin functional group is coupled through its carboxy terminus to the linker.

116. (currently amended) The compound of claim 110 wherein biotin[[R]] is separated from A-X by up to 100 angstroms.

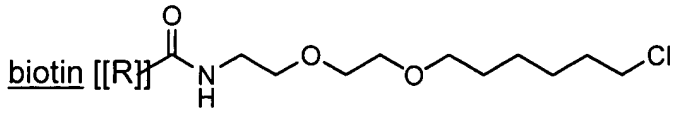
117. (currently amended) The compound of claim 110 wherein biotin[[R]] is separated from A-X by up to 500 angstroms.

119. (currently amended) A compound prepared by the method of claim 107 wherein the compound is:



120. (currently amended) A compound of formula (I): biotin[[R]]-linker-A-X, wherein biotin[[R]] is a ~~one or more~~ functional group[s], wherein the linker is a branched or unbranched carbon chain comprising from 2 to 30 carbon atoms, which chain optionally includes one or more double or triple bonds, and which chain is optionally substituted with one or more hydroxy or oxo (=O) groups, wherein one or more of the carbon atoms in the chain is optionally replaced with a non-peroxide -O-, -S- or -NH-, wherein the linker-A separates biotin[[R]] and X by at least 11 atoms, wherein A is $(CH_2)_n$ and n = 2-10, wherein A-X is a substrate for a dehalogenase, wherein X is a halogen, and wherein ~~R is a~~ the biotin functional group is coupled through its carboxy terminus to the linker.

121. (Previously Presented) A compound of formula (II):



Authorization for this Examiner's Amendment was given by telephone by Applicants' agent, Ms. Janet Embretson, on November 27, 2006.

2. The following is an examiner's statement of reasons for allowance. The prior art neither teaches nor suggests the compounds of claims 107 and 109-122 (compounds in which the linker is covalently linked to biotin, biotin being the functional group) or methods of preparing these compounds by the methods of claims 107 or 109. As previously discussed in the Office action of March 14, 2006, Bennetau et al. (WO 01/53303, see corresponding U.S. Application No. 2003/0166957) disclose a compound comprising a functional group (a carbon-carbon double bond) and a halide (chloride). The functional group and halide are separated by at least 12 atoms, the linker comprises between about 2 and about 30 atoms in an unbranched chain, and the molecule, between the linker and the halide, comprises at least four CH_2 groups (see Fig. 2, compound 6).

Morita et al. (US 4,818,807) disclose compounds (ferroelectric liquid crystal polymers) comprising a functional group (phenyl groups, aromatic rings) and a halide (bromide). The functional group and halide are separated by at least 12 atoms, the linker comprises between about 2 and about 30 atoms in an unbranched chain, and the molecule, between the linker and the halide, comprises at least four CH_2 groups. The linker also comprises an oxo group and an oxygen heteroatom (see col. 3, lines 48-49, and col. 7, lines 29-68). The compound is made by reacting a molecule of the formula Z-linker-A-X, in which Z is Br and linker-A is a 10- to 12-carbon alkyl chain with the alcohol form of the benzene-ring-containing compounds (Y = H) (see col. 3, lines 48-49, col. 7, lines 29-68 and Examples 1, 4 and 5 in cols. 11-15).

Lustoň et al. (CS 259396) disclose a compound (an inhibitor of photodegradation for polymers) comprising a functional group (a piperidine ring) and a halide (bromide). The functional group and halide are separated by at least 12 atoms, the linker comprises between about 2 and about 30 atoms in an unbranched chain, and the molecule, between the linker and the halide, comprises at least four CH_2 groups. The linker also comprises an oxygen heteroatom (see Abstract, Formula I). The compound is made by reacting a molecule of the formula Z-linker-A-X, in which Z is Br and linker-A is a 12-carbon alkyl chain with the alcohol form of the piperidine compound (Y = H) (see pp. 2, 4 and 10 of the English translation).

Morzycki et al. ("Synthesis of dimeric steroids as components of lipid membranes," Tetrahedron 53(30):10579-10590, 1997) disclose a compound comprising a functional group (a steroid) and a halide (iodide). The functional group and halide are separated by at least 11 atoms, the linker comprises between about 2 and about 30 atoms in an unbranched chain, and the molecule, between the linker and the halide, comprises at least four CH_2 groups (see p. 10582, compound 11). The functional group, a steroid, is a lipid and a drug.

3. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

rk/2006-11-27

JON WEBER
SUPERVISORY PATENT EXAMINER